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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carlos PICORNELL DARDER

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1616

Mail Stop Non Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. CARMEN MOLINA-MILLÁN

SIR:

The undersigned, Dr. Carmen Molina Millán declares as follows:

1. I am an employee of LICONSA and an expert in the field of pharmaceutical technology. I am a graduate in Chemical Sciences and hold a Ph.D. in Pharmacy from the University of Madrid (Universidad Complutense de Madrid).

2. I am the same Dr. Carmen Molina-Millán who previously submitted a declaration in this matter.

3. I have been asked to fairly reproduce the first step of Example 11 of PCT patent application WO 96/01624 ("WO '624") to obtain the enteric coating layered pellets before these pellets are compressed to form tablets (second step of Example 11).

4. According to WO '624, the make-up of the coated pellets (not the tablets) is as follows:

Example 11

Enteric Coated Pellets	
Core material (no separating layer)	500 g
Methacrylic acid copolymer	500 g
Triethyl citrate	150 g
Mono- and diglycerides	25 g
Polysorbate 80	2.5 g
Purified water	978 g

The core material is produced as in Example 1 and in Example 10 of WO '624. Example 1 and Example 10 set forth the procedure for producing the respective core materials as follows:

Example 1

Core Material	
Lansoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	82 g
Sodium lauryl sulfate	3 g
Purified water	1 600 g

Suspension layering is performed in a fluid bed apparatus using bottom spray technique. Lansoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds are in the range of 0.25 to 0.35 mm.

Example 10

Core Material	
Pantoprazole	100 g
Sugar sphere seeds	200 g
Hydroxypropyl cellulose	25 g
Purified water	607 g

Suspension layering is performed in a fluid bed apparatus. Pantoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

5. Since Example 11 does not explicitly describe a procedure for producing the enteric coating layer. I have assumed that the procedure should be similar to those procedures described in Examples 1 and 10 of WO '624, but without the step of forming the inert separating layer.

6. As observed, from an experimental point of view, Examples 1, 10 and 11 lack many technical details, which I have completed following my best professional knowledge. To produce both the first coating and the enteric coating I employed a standard bottom spray fluidized bed apparatus (model HKC5), and usual operating conditions: air volume of 320-340 m^3/hour; pressure 1.0-1.2 bar; product temperature 38°C. As the methacrylic acid copolymer I have used Eudragit L30 D55, which is a standard methacrylic acid copolymer used for enteric coatings and the same copolymer used in Example 1 of the presently pending patent application under examination. Serial No. 09/491,624.

7. There are many types of "mono- and diglycerides". Example 11 fails to identify which was used. I have selected glyceryl monoestearate 40-55, which according to the Handbook of Pharmaceutical Excipients, Fourth Edition, page 264 (ISBN-0853694729) contains at least a 40% of monoglycerides and 30-45% of diglycerides.

8. The amount of Polysorbate 80 specified in Example 11 is not enough to completely dissolve or disperse the selected mono-diglyceride (Polysorbate 80 acts as a non-ionic surfactant for dispersing oils in water), and therefore I have increased the amount of Polysorbate 80 until reaching a good solution/dispersion of the mono-diglyceride.

9. For a proper operation of the fluidized bed apparatus used, it is necessary to employ larger quantities of materials than those explicitly described in the Examples. Accordingly, I have increased the amounts of the different components, but maintained the same proportions of the components of Examples 1, 10 and 11 (except in the case of the Polysorbate 80 for the reasons that I have explained above). The remainder of the details not mentioned above literally correspond to the specifications set forth in Examples 1, 10 and 11 of WO '624.

10. I obtained a "core material" according to each of Examples 1 and 10 without having significant problems. Both core materials had a white-creamy color prior to the application of the enteric coating layer.

11. However, serious problems were encountered when I proceeded to apply the enteric coating layer of Example 11. The rate of spraying of the enteric coating solution/dispersion had to be slower than usual (at about 6-8 g/minute) because the pellets showed an increasing tendency to stick. Also, the pellets began to exhibit a brown color which became darker with time.

12. Figures 1 and 2 of Annex 1 hereto show the evolution of the color of the pellets during the enteric coating process:

Lansoprazole pellets (core material of Example 1)

Sample A - pellets prior to application of the enteric coating.
Sample B - pellets after 1 hour of spraying of the enteric coating.
Sample C - pellets after 2 hours of spraying of the enteric coating.
Sample D - pellets after 5 hours of spraying of the enteric coating.

Pantoprazole pellets (core material of Example 10)

Sample E - pellets prior to application of the enteric coating.
Sample F - pellets after 2 hours of spraying of the enteric coating.
Sample G - pellets after 4 hours of spraying of the enteric coating.
Sample H - pellets after 6 hours of spraying of the enteric coating.

13. The strong brown color of the obtained pellets shows a degradation of the active ingredient, and such pellets are completely unacceptable in a pharmaceutical composition.

14. The results obtained in the practice of Example 11 of WO '624 were not surprising because the prior art, for instance EP 0247983 and EP 244380 cited in the pending patent application, taught that an inert separating layer must be placed between the core material and the outer enteric coating layer to avoid the contact between the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole, etc.) and the acidic component (methacrylic copolymer) of the enteric layer because the benzimidazole compounds are acid labile, i.e. not stable in acidic medium, and once in contact with acidic compounds they undergo rapid degradation and develop a strong color.

15. Figure 3 of Annex 1 shows the evolution of the color during the enteric coating process of lansoprazole pellets prepared according to Example 1 of the presently pending application.

Lansoprazole pellets (Example 1 of the present application)

Sample L1 - pellets prior to application of the enteric coating.
Sample L2 - pellets 1 hour after spraying of the enteric coating.
Sample L3 - pellets after 2 hours of spraying of the enteric coating.
Sample L4 - pellets after 3 hours of spraying of the enteric coating.
Sample L5 - pellets after 4 hours of spraying of the enteric coating.
Sample L6 - pellets after 5 hours of spraying of the enteric coating.
Sample L7 - pellets after 6 hours of spraying of the enteric coating.
Sample L8 - finished pellets.

The pellets obtained according to Example 1 of the presenting pending application do not have an inert separating layer but maintained a stable white-creamy color during the full process and, according to the data shown in Example 1, are stable during storage for several months thereafter, even when exposed to high temperature and humidity conditions.

16. In my opinion, the obtained results show that Example 11 of WO '624 does not enable one to prepare the oral pharmaceutical preparations claimed in the presently pending patent application. In fact, it is my conviction that the disclosure of WO '624, including Example 11, does not enable one to obtain any acceptable lansoprazole or pantaprazole oral pharmaceutical composition, due to the strong color developed as a consequence of the rapid acidic degradation of the active compound.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: July 6, 2006

Dr. Carmen Molina-Millán